U.S. Serial No.: 09/305,738 Docket No.: 2324-7028US1

REMARKS

Status Of Claims

Applicants respectfully request entry of this Amendment and reconsideration of the application. Claims 1-26 and 39-45 have been previously canceled. Claim 35 is canceled herein. Upon entry of this Amendment, claims 27-34 and 36-38 are currently amended. New claims 46-90 are added herein. No new matter is added.

Examiner Interview

Applicants thank the Examiner for the courtesy extended to the undersigned during an Examiner Interview which occurred on May 13, 2004.

Applicants herein provide details as discussed regarding the production process, the results of separation processes upon particle size distribution, as well as further comments regarding the disclosures of O'Shannessy I and II.[1]

As discussed during the interview, the "dust"[2], fines and small particles of both O'Shannessy I and II are removed by flotation in acetonitrile and discarded. O'Shannessy I discloses:

> Particles which passed through the 25 μm sieve were extensively defined ...[3]

O'Shannessy II discloses:

> In all cases, dust was removed by flotation in acetonitrile.[4]

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[1] O'Shannessy I refers to the article of O'Shannessy, Ekberg and Mosbach, Molecular Imprinting of Amino Acid Derivatives at Low Temperature (0°C) Using Photolytic Homolysis of Azobisnitriles, Anal. Biochem., 177, 144-149 (1989). O'Shannessy II refers to the article of O'Shannessy, Ekberg, Andersson and Mosbach, Recent Advances In The Preparation And Use Of Molecularly Imprinted Polymers For Enantiomeric Resolution Of Amino Acid Derivatives, J Chom. 470, 391-399 (1989).

[2] O'Shannessy II, p. 353.

[3] O'Shannessy I, p. 145.

[4] O'Shannessy II, p. 353.

The flotation process, discussed in detail *infra*, employed in the work disclosed in O'Shannessy I and II was utilized to "extensively define" and "remove" "dust", fines and small particles from the particle distribution resulting from sieving the crushed block polymer. This procedure produces a particle distribution having an upper limit of 25 μm diameter. In the O'Shannessy I and II process, flotation (i.e., settling) is used to separate the desired larger particles from the smaller particles which were to be removed. The "dust", fines and small particles are discarded. *See* Declaration Under 37 C.F.R. § 1.132 By George B. Sigal, Ph.D. (Sigal Declaration, filed November 5, 2003).

The settling process produces a collection of larger settled particles and a turbid supernatant liquid in which the smaller particles are suspended and which are separated from the larger particles. During each repetition of the separation process ("defining"), the supernatant and the particles it contains are discarded leaving behind in the container the larger particles which have settled.

By sieving at 25 μm, the particle diameter of 25 μm would be understood to be the upper limit of the particle distribution which passed through the sieve. The phrase "extensively defined"[5] would be understood by a person having ordinary skill in the pertinent art to mean multiple repetitions of the flotation process were preformed to achieve a narrow particle distribution closely bounding the 25 μm particle upper limit diameter of the distribution resulting from the sieving process. Thus, the technique of "extensively" defining and removing "dust", fines and small particles would be understood to mean separating and discarding "dust", fines and those particles which have a diameter not within a desired tolerance below 25 μm (Sigal Declaration, p. 3). Thus, a person having ordinary skill in the pertinent art would understand

[5] O'Shannessy I, p. 14:.

O'Shannessy I and II to disclose the removal and discarding of "dust", fines and small particles not within a desired tolerance around 25 μm. Applicants assert the disclosures of O'Shannessy I and II do not teach or suggest the utilization of the "dust", fines and smaller particles which are contained in the discarded supernatant liquid which are substantially below 25 μm (Sigal Declaration, p. 3). Applicant's claims recite a range of particles which were discarded in O'Shannessy I and II.

As discussed during the interview, in view of the above Applicants' current clams are not anticipated and not obvious over O'Shannessy I and II whether considered alone or in combination.

REJECTION UNDER 35 U.S.C. § 112

Claims 34-38 stand rejected under 35 U.S.C. § 112, second paragraph. Applicants appreciate the Examiner's clarification of the rejection of record.

As discussed during the Examiner Interview, independent claim 34 from which claims 36-38 depend has been amended to recite:

> Claim 34 (Currently Amended): A method for assaying a drug molecule in a fluid, comprising the steps of:
>
> providing a fluid sample with a drug molecule,
>
> adding a known amount of said drug molecule to said sample,
>
> contacting said sample with an artificial antibody comprising a crosslinked polymer prepared by molecular imprint polymerization and having a binding site having specificity for said drug molecule, wherein said artificial antibody has a particle size of less than about five microns binding said drug molecule with said artificial antibody.

Applicants respectfully assert that amended claim 34 is definite and respectfully request the withdrawal of the rejection of claims 34-38 under 35 U.S.C. § 112.

DOUBLE PATENTING REJECTION

Claims 27-38 remain rejected under the judicially created doctrine of obviousness-type double patenting.

Applicants again offer to file a terminal disclaimer upon the Examiner's statement of allowable subject matter.

REJECTION UNDER 35 U.S.C. §§ 102 AND 103

Further to the technical discussion *supra* and in accordance with the discussion of the Examiner Interview, Applicants herein provide technical background regarding the O'Shannessy I and II references. Klaus Mosbach, Ph.D., is an Inventor of this application and a named author of both O'Shannessy I and II. Dr. Mosbach explains the procedure disclosed in O'Shannessy I and II includes the following steps: (1) The imprinted block polymer was crushed using mortar and pestle to form crushings; (2) the crushings were sieved through a 25 μm sieve; (3) collected in a beaker of liquid (e.g., acetonitrile;) and (4) allowed to settle forming a mass of particles of larger size which have settled to the bottom of a beaker and also forming a turbid supernatant liquid which contained suspended particles including the "dust", fines and small particles. (5) The turbid supernatant liquid containing the "dust", fines and small particles was poured off and discarded. (6) The flotation process (i.e., settling process) process was typically repeated at least 2, or 3 times, or until the "dust", fines and smaller particles were "extensively defined" (i.e., sufficiently removed) from the desired larger particles within a close tolerance of the 25 μm sieved value.

During each repetition of the flotation ("definition"), the supernatant liquid carrying the fines and smaller particles was discarded. As set forth *supra*, Dr. Mosbach relates the work disclosed in O'Shaughnessy I and II utilizing flotation successfully achieved a selection of retained (i.e., settled) particles having a diameter distribution closely grouped around 25 μm. As such "dust", fines and small particles were successfully separated from the desired particle grouping of around 25μm and then discarded. Particles the size of those now claimed by applicants were removed by flotation, contained in the supernatant, and discarded where the supernatant was poured off.

The particle separation technique, finds a basis in the following theory: Particles when suspended into a liquid whose density is greater than the liquid will tend to sink due to gravitational forces. The speed at which they sink depends on many things, for example, the size and shape of the particles. Ronald Probstein, in the second edition of his book Physicochemical Hydrodynamics (1994), explains this sedimentation under gravity. As shown in Applicants' figures below, particles that start uniformly distributed in a beaker will start to accumulate on the bottom, clearing the uppermost of the liquid first. Larger particles settle faster. The velocity U at which spherical particles settle is $d^2 ((\rho_p / \rho_L) - 1)\, g / (18\, \nu)$, where d is the diameter, ρ_p is the density of the particles, ρ_L is the density of the liquid, g is the acceleration of gravity, and ν is the kinematic viscosity of the liquid.

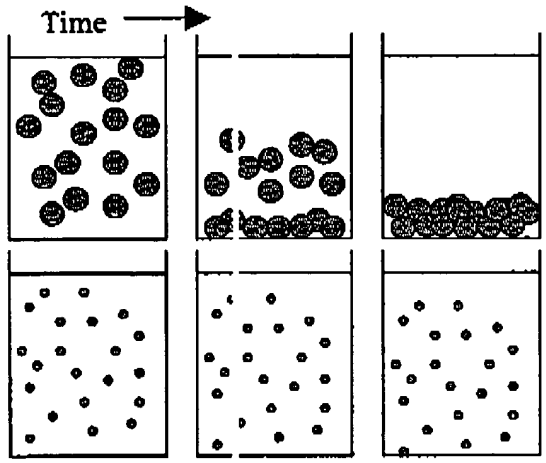

Figure 1: Six beakers with 2 different particle sizes at 3 different time points are shown to illustrate sedimentation rates.

The method of particle separation utilized in O'Shannessy I and II for "defining" removed the "dust", fines and small particles which were not within the desired 25 μm diameter ± desired tolerance (i.e., lower bound of desired diameters below 25 μm). Removing the "dust", fines and smaller particles by flotation or "defining" entails waiting until the large particles have settled, then pouring off the liquid (supernatant liquid) that contains the smaller particles. This process may be repeated as many times as desired to "extensively" define the sample.

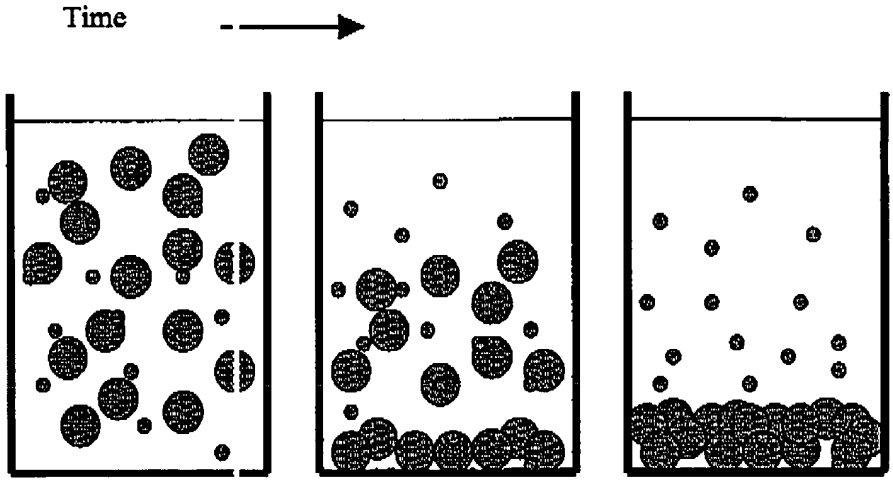

Figure 2: Three beakers showing the effect of flotation separation over time on mixed particles at three different times to illustrate sedimentation rates.

Figure 2, *supra* illustrates the aforementioned separation ("flotation") technique disclosed by O'Shannessy I and II which results in a turbid supernatant having the fines, dust and smaller particles.

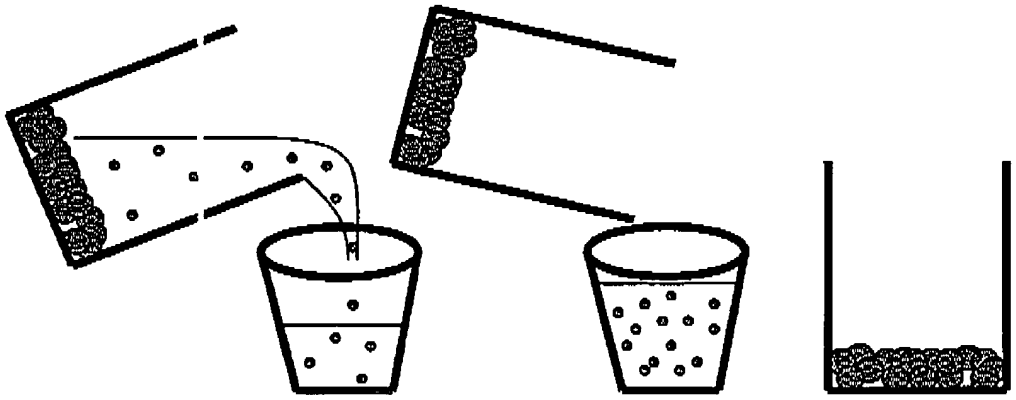

Figure 3: Illustration of the pouring off of the supernatant, thus removing "dust", fines, and small particles and leaving behind the settled larger particles.

Figure 3, *supra*, illustrates pouring the turbid supernatant from the sedimentation beaker for disposal of the "dust", fines, and small particles. The last beaker represents the settled larger particles where the supernatant and the small particles of the supernatant have been removed.

The figures 2 and 3 represent one repetition of the flotation process. As previously discussed the settling (flotation) technique may be repeated as many time as required to achieve "extensively defined", i.e. to achieve the removal of particles with the exception of those having a diameter closely grouped around 25 μm and within a desired tolerance.

Distinguishing Applicants' Claimed Particle Diameter Ranges Over O'Shannessy I and II

In view of the above, Applicants assert at least one fundamental difference between Applicants' claimed invention and the work disclosed in O'Shannessy I and II is that particles which were smaller than the particles of the 25 μm closely bounded group were discarded through the procedures of O'Shannessy I and II.

As the smaller particles are discarded in O'Shannessy I and II are removed and discarded, a person having ordinary skill would be taught to use, the "dust", fines and smaller particles claimed by Applicants in their claimed invention.

Each of Applicants' independent claims recite a particle size of "less than about five microns". Applicants claim a range of particles not disclosed by either O'Shannessy I or II. Further, Applicants assert there is no disclosure in O'Shannessy I or II regarding the utilization of a particle size of "less than about five microns". In contrast, particles of this size would have been discarded with the supernatant liquid through the procedures disclosed in O'Shannessy I and II.

Thus, neither O'Shannessy I or II, whether considered alone or in combination, disclose all claimed elements of Applicants' claimed invention and do not teach or suggest Applicants' claimed invention. Further, by discarding the "dust", fines, and small particles, O'Shannessy I and II respectively teach away from Applicants' claimed invention. In view of the above, O'Shannessy I and II whether considered separately, or in combination, do not anticipate and do not make obvious Applicants' claimed invention.

Further to the Examiner's comments, Applicants hereby clarify the record regarding paragraph 15 of the Declaration Under 37 C.F.R. § 1.132 By George B. Sigal, Ph.D. The Sigal Declaration recites:

> 15. ... The references do not foresee, teach or suggest the utility of the particulates of 5μm or less. Furthermore, the O'Shannessy references teach away from the claimed size range of particles by explicitly teaching the removal of particles much smaller than 25 μm prior to column packing.

In view of the above, Applicants' assert that the Sigal Declaration is technically consistent and an accurate characterization of the disclosures of O'Shannessy I and II.

In view of the above, the Examiner's specific rejections are traversed further *infra*.

Alternative Rejections Under 35 U.S.C. § 102(b) And 103(a)

Claims 27-38 stand rejected alternatively under 35 U.S.C. § 102(b), or under 35 U.S.C. § 103(a) over U.S. Patent No. 5,110,833 (U.S. '833). The 35 U.S.C. § 102(b) rejections of the Office Action of May 5, 2002, are maintained in regard to U.S. '833, which in turn maintains the rejection of the Office Action of August 7, 2001.

Applicants respectfully traverse. Each of Applicants' independent claims recite a particle size of "less than about 5 microns".

U.S. '833 discloses:

> Polymer preparation: The polymers were prepared as described D. J. O'Shannessy, B. Ekberg and K. Mosbach Anal. Biochem. 177, 144 (1989) and D. J. O'Shannessy, B. Ekberg, L. I. Andersson and K. Mosbach J. Chrom. 470, 391 (1989)) with ethylene dimethracrylate as crosslinker and either methacrylic acid of methyl methacrylate as functional monomer.

(U.S. '833, col. 5, lines 29-33). Thus, the '833 patent expressly discloses that "The polymers were prepared as described" in O'Shannessy I and II.

As discussed above, neither O'Shannessy I or II disclose "a particle size of less than about 5 microns". Thus, Applicants assert that U.S. '833 does not disclose the claimed invention. It follows, U.S. '833 which utilizes the techniques of O'Shannessy I or II extensively defines the 25 μm particles and also discards "dust", fines and small particles.

The disclosures of '833, O'Shannessy I and II whether considered separately or in combination do not disclose the claimed ranges of "less than 5 microns".

Further, U.S. '833 does not disclose biocompatibility. For illustration, Applicants assert a typical human red blood cell is about 5 microns in diameter. "Applicants disclose that preferably, they must be of the size not more than 5 μm or the size of normal biological antibodies, most preferred 10-100 nm" (*see* specification, on page 4, at lines 21-25). Thus, Applicants respectfully assert the characteristics, properties and invention of the claimed range of particles "less than 5 microns" is not inherent in the disclosure of O'Shannessy I and II.

In view of the above, U.S. '833 does not disclose all of the elements of the claimed invention either expressly or inherently. Thus no case of anticipation exists under 35 U.S.C. § 102(b) over U.S. '833. Applicants respectfully request that the Examiner withdraw the rejection of claims 27-38 under 35 U.S.C. § 102(b). Furthermore, '833, whether alone or in combination with O'Shannessy I or II, does not teach or suggest all claimed elements of Applicants' invention and no prima facie case of obviousness under 35 U.S.C. § 103(a) exists. By following the polymer preparation of O'Shannessy I and II, U.S. '833 teaches away from Applicants' claimed

invention. Thus Applicants request the withdrawal of all rejections under 35 U.S.C § 102 and § 103.

CONCLUSION

In view of the above, Applicants respectfully request that the rejection of claims 27-38, under 35 U.S.C. § 102(b) or alternatively under 35 U.S.C. § 103(a), and of claims 34-38 under 35 U.S.C. § 112 be withdrawn. Applicants assert that the above-identified application is in condition for allowance and request such action at this time.

AUTHORIZATIONS

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deport Account No. 13-4503, Order No. 2324-7028US1. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
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